Amendment to the Specification:

Please amend the paragraph after the title on page 1 with the following paragraph:

[0001] This application is a continuation of application number 09/877,957 which is a continuation-in part of application number 09/568,121, which is a continuation-in part of non-provisional application number 09/272,109, filed March 19,1999, which claimed priority under Section 119(e) to provisional application number 60/078,649, filed March 19, 1998. The 09/568,121 application also claims priority under Section 119(e) to provisional application numbers 60/133,304, filed May 10,1999, 60/133,305 also filed May 10, 1999, 60/187,448 filed March 7, 2000, and 60/193,054 filed March 29, 2000. In addition, the present application ~~cliams~~ claims priority under Section 119(e) to provisional application number 60/210,871 filed June 8, 2000. The contents of the foregoing provisional and non-provisional applications are hereby incorporated by reference.

The paragraph beginning on line 5 of page 7 has been amended as follows:

[0018] One embodiment of the invention provides a method of making an amido-containing metallacycle comprising combining an amount of an ~~a-aminoacid-N-carboxyanhydride~~ α-aminoacid-N-carboxyanhydride monomer with an initiator molecule comprising a low valent transition metal-Lewis Base ligand complex so that an amido-containing metallacycle is formed.

The paragraph beginning on line 17 of page 8 has been amended as follows:

[0022] A related embodiment is method of initiating an ~~a-amino acid -N-carboxyanhydride~~ α-aminoacid-N-carboxyanhydride monomer polymerization by combining an NCA monomer with an initiator molecule comprising an amido-containing metallacycle, which contains a nucleophilic alkyl amido group stabilized by a rigid chelate and a non-nucleophilic proton-accepting group. In preferred versions, the proton-accepting group is selected from the group of ~~amide~~ a sulfonamidate, an ~~amido-amidate~~ amidate having an ~~extracyclic nitrogen~~ exocyclic

carbonyl, ~~an amido-ureate~~ a ureate, ~~and amido-carbamate~~ a carbamate, or an ~~amido-aldimate~~ aldimate.

The paragraph beginning on line 25 of page 17 has been amended as follows:

[0055] The reaction chemistry of ~~a-amino acid-N-carboxyanhydrides~~ α-aminoacid-N-carboxyanhydride (NCAs) has been under study since these molecules are potential precursors to sequence specific peptides, polypeptides, and other amino acid containing compounds. H.R. Kricheldorf, *a-Aminoacid-N-Carboxyanhydrides and Related Materials*, Springer-Verlag, New York, (1987); H.R. Kricheldorf, in *Models of Biopolymers by Ring-Opening Polymerization*, Penczek, S. Ed., CRC Press, Boca Raton, (1990). NCAs are attractive peptide building blocks since they are readily prepared from amino acids and since they show no racemization at the chiral [a-carbon] α-carbon either during preparation or in subsequent reactions. W.E. Hanby, et al., *Nature*, 161:132 (1948); A. Berger, et al., *J. Am. Chem Soc.*, 73:4084-4088 (1951). Utilization of NCAs, however, has been limited because of their complicated reactivity and tendency to uncontrollably polymerize.

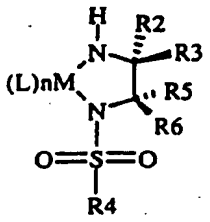
The paragraph beginning on line 29 of page 24 has been amended as follows:

[0070] One embodiment of the invention provides a method of making an amido-containing metallacycle comprising combining an amount of an ~~a-aminoacid-N-carboxyanhydride~~ α-aminoacid-N-carboxyanhydride monomer with an initiator molecule comprising a low valent transition metal-Lewis Base ligand complex so that an amido-containing metallacycle is formed. Formation of these initiators results from the unprecedented reaction of an NCA monomer with a low valent metal-Lewis base complex such as a zerovalent nickel complex bipyNi(COD); bipy = 2,2'-bipyridyl, COD = 1,5-cyclooctadiene. This reaction is similar to the oxidative-addition of cyclic anhydrides to zerovalent nickel which yields divalent nickel metallacycles (see equation 6 below). E. Uhlig, et al., ["] "Reaktionen cyclischer Carbonsaeureanhydride mit [(a,a=-Dipyridyl)-(cyclooctadien-1,5)-nickel"] (α,α=-Dipyridyl)-(cyclooctadien-1,5)-nickel" *Anorg. Allg. Chem.*, 465:141-146 (1980); K. Sano, et al., "Preparation of Ni- or Pt-Containing Cyclic Esters by Oxidative Addition of Cyclic Carboxylic Anhydrides and Their Properties" *Bull. Chem. Soc.*

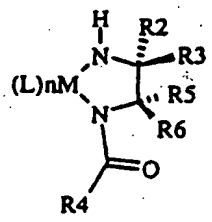
Jpn., 57:2741-2747 (1984); A.M. Castaño, et al., "Reactivity of a Nickelacycle Derived from Aspartic Acid: Alkylations, Insertions, and Oxidations" *Organometallics*, 13:2262-2268 (1994).

The paragraph beginning on line 15 of page 36 has been amended as follows:

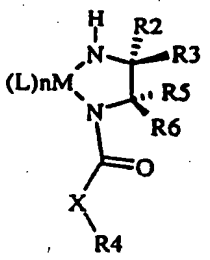
[0096] The success of the ruthenium initiator described above shows that many other initiator structures besides the amido-amidate (or amido-alkyl) metallacycles described above can be used for controlled NCA polymerizations. The key features that appear to be required for successful initiator formation are those that were previously identified, namely: a metallcycle containing a nucleophilic alkyl amido group, stabilized by a rigid chelate, and a proton-accepting group on the other end of the metallacycle that allows the chain-end to migrate off the metal, but which is also non-nucleophilic. The new feature shown in this disclosure is that the "proton-accepting group" can be something different that the originally discovered amido-amidate unit. This original structure, and some possible alternatives that have potential to form good initiators, are shown in Figure 1. Note that many ~~amido-conatining~~ amido-containing metallacycles can be functionally equivalent good initiators, such as the following new structures:



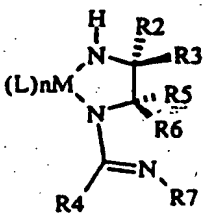
amido-sulfonamidate aldimate (shown by ruthenium compound 1)



amido-amidate ([extracyclic] exocyclic amide)



amido-ureate (X=NH) amido-amido carbamate (X=O)



wherein R2, R3, R5, and R6 are each independently hydrogen or any organic substituent not bearing free amine, hydroxyl, carboxylic acid, sulfhydryl, isocyanate, imidazole, or other highly protic or nucleophilic functionality, e.g. C1-C12 alkyl or aryl groups such as phenyl. Similarly, R4 and R7 are each any organic substituent not bearing free amine, hydroxyl, carboxylic acid, sulfhydryl, isocyanate, imidazole, or

other highly protic or nucleophilic functionality. A most preferred Lewis base donor ligand, L, is p-cymene and the most preferred low valent transition metal, M, is ruthenium.

The paragraph beginning on line 15 of page 38 has been amended as follows:

[00101] In a preferred embodiment of the method of adding an aminoacid-N-carboxyanhydride (NCA) to a polyaminoacid chain having an amido containing metallacycle end group, the metal group of the amido containing metallacycle is a transition metal selected from the group consisting of nickel, palladium, platinum, cobalt, rhodium, iridium and iron and the Lewis Base ligand is selected from the group consisting of pyridyl ligands, diimine ligands, bisoxazoline ligands, alkyl phosphine ligands, aryl phosphine ligands, tertiary amine ligands, isocyanide ligands, and cyanide ligands. In specific embodiments of the invention, the NCA is an ~~a-aminoacid-N-carboxyanhydride~~ α-aminoacid-N-carboxyanhydride selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

The paragraph beginning on line 8 of page 42 has been amended as follows:

[00109] In yet another preferred embodiment of this method, the first ~~a-aminoacid-N-carboxyanhydride~~ α-aminoacid-N-carboxyanhydride monomer is an NCA is an ~~a-aminoacid-N-carboxyanhydride~~ α-aminoacid-N-carboxyanhydride selected from the group consisting of side-chain protected NCA formed from arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, histidine, lysine, methionine, serine, threonine, tryptophan, and tyrosine or an amino acid side chain selected from the group consisting of side-chain NCA formed from alanine, glycine, isoleucine, leucine, phenylalanine, proline and valine.

The paragraph beginning on line 27 of page 52 has been amended as follows:

[00135] As discussed above, ~~a-Amino acid-N-carboxyanhydrides~~ α-Amino acid-N-carboxyanhydrides (NCAs) were reacted with zerovalent nickel complexes of the type $L_2Ni(COD)$ to yield metallacyclic oxidative addition products.

These oxidative addition reactions were found to result in the addition across either the O-C_5 or the O-C_2 bond of the NCAs, ultimately giving, after addition of a second equivalent of NCA, chiral amido-amidate nickelacycles. The origins and structures of these complexes were elucidated by use of selectively ^{13}C labeled NCA reagents. Stable metallacycles were obtained when L = PPh_3. When other donor ligands were used, the metallacycle intermediates were found to quickly react with additional NCA molecules to form polypeptides in quantitative yield and with narrow molecular weight distributions. These reactions provide a facile route to unusually stable metallacyclic amido-containing nickel intermediates.

The paragraph beginning on line 19 of page 70 has been amended as follows:

[00173] Other diblock and triblock copolymers were prepared by a procedure identical to that described above for either PZLL-*b*-PBLG and PBLG-*b*-PZLL-*b*-PBLG, except that either different monomers, or different amounts of monomers, were used for the individual polymerization reactions. Examples are given in Tables 4 ~~(abovee)~~ (above) and Table 5 (below). The nature of the amino acid monomer was found to be unimportant in limiting the effectiveness of these polymerizations. All amino acid NCAs tried were incorporated into block copolypeptides in any sequential order, as determined by the order of addition to the initiator. Representative monomers include, but are not limited to: the naturally occurring L-amino acids, naturally occurring D-amino acids, ~~a-disubstituted a-amino~~ *α*-disubstituted *α*-amino acids, racemic ~~a-amino~~ *α*-amino acids, and synthetic ~~a-amino~~ *α*-amino acids. Block copolypeptides could be prepared using initiators other than (2,2=-bipyridyl)Ni(COD). The initiators given in Tables 7 and 8 below (except those that gave no yield of polymer) all were able to prepare block copolypeptides.

The paragraph beginning on line 3 of page 73 has been amended as follows:

[00176] The range of substituents (R) which can be placed on the amido-containing metallacycles was investigated. These include the side chain functions found in amino acids themselves (e.g. R = $CH_2C_6H_5$ from phenylalanine, R = $CH_2CH(CH_3)_2$, or R = $CH_2CH_2CO_2CH_2C_6H_5$ from g-benzylglutamate), and should thus include any organic moiety attached to an ~~a-amino~~ *α*-amino acid.